Sleep-disordered breathing and periodic limb movements in narcolepsy with cataplexy: A systematic analysis of 35 consecutive patients

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Abstract: Background: Disturbed sleep is a core feature of narcolepsy with cataplexy (NC). Few studies have independently assessed sleep-disordered breathing (SDB) and periodic limb movements (PLMs) in non-homogeneous series of patients with and without cataplexy. We systematically assessed both SDB and PLMs in well-defined NC patients. Methods: We analyzed the clinical and polysomnographic features of 35 consecutive NC patients (mean age 40 ± 16 years, 51% males, 23/23 hypocretin-deficient) to assess the prevalence of SDB (apnea-hypopnea index >5) and PLMs (periodic leg movements in sleep (PLMI) >15) together with their impact on nocturnal sleep and daytime sleepiness using the multiple sleep latency test. Results: 11 (31%) and 14 (40%) patients had SDB and PLMs, respectively. SDB was associated with older age (49 ± 16 vs. 35 ± 13 years, p = 0.02), higher BMI (30 ± 5 vs. 27 ± 6, p = 0.05), and a trend towards higher PLMI (25 ± 20 vs. 12 ± 23, p = 0.052), whereas PLMs with older age (50 ± 16 vs. 33 ± 11 years, p = 0.002) and reduced and fragmented sleep (e.g. sleep efficiency of 82 ± 12% vs. 91 ± 6%, p = 0.015; sleep time of 353 ± 66 vs. 395 ± 28, p = 0.010). SDB and PLMs were also mutually associated (p = 0.007), but not correlated to daytime sleepiness. Conclusions: SDB and PLMs are highly prevalent and associated in NC. Nevertheless, SDB and PLMs are rarely severe, suggesting an overall limited effect on clinical manifestations.

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Title Page

Title: Sleep disordered breathing and periodic limb movement disorder in narcolepsy with cataplexy: a systematic analysis of 36 consecutive patients.

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Abstract

Background: Disturbed nocturnal sleep is a core feature of narcolepsy with cataplexy (NC). Several studies have assessed independently sleep disordered breathing (SDB) and periodic limb movement disorder (PLMD) in mostly non-homogeneous populations of narcoleptic patients.

The aim of this study was therefore to systematically assess both SDB and PLMD in patients with narcolepsy, cataplexy, and hypocretin-1 deficiency.

Methods: We analyzed clinical and polysomnographic features of 36 consecutive NC patients (mean age of 39±16 years, 50% males) in order to assess the prevalence of SDB (AHI>5) and of PLMD (PLMI>15) together with their impact on nocturnal sleep and daytime sleepiness at the MSLT.

Results: Eleven (31%) and 14 (39%) patients had SDB and PLMD, respectively. SDB was associated with older age (49±5 vs. 35±3 years; p=0.02) and higher BMI (30±1 vs. 26±1 kg/m2; p=0.04), whereas PLMD with older age (50±4 versus 32±2 years, p=0.001) and sleep fragmentation (e.g. sleep efficiency of 82±12% vs 92±6%, p=0.01). SDB and PLMD were also mutually associated (p=0.006), but not correlated to daytime sleepiness.

Conclusions: SDB and PLMD are highly prevalent and associated in NC patients. Nevertheless, SDB and PLMD in NC appears to be rarely severe, suggesting an overall limited effect on clinical manifestations.

Introduction

Narcolepsy with cataplexy (NC) is characterized by excessive daytime sleepiness (EDS), cataplexy, sleep paralysis, and hallucinations. NC is a hypersomnia of central origin, pathophysiologically associated with the loss of hypocretin (orexin) producing neurons in the hypothalamus [1].

Besides EDS with daytime naps, NC patients typically suffer from nocturnal sleep fragmentation with reduced sleep efficiency, numerous awakenings and larger representation of wakefulness after sleep onset and of Non-REM sleep stage 1, resulting in a total sleep time per 24 hours which is comparable to controls [2]. Comorbid sleep disordered breathing (SDB) [3-5] and periodic limb movement disorder (PLMD) [6-10], both potentially enhancing nocturnal sleep disruption, frequently occur in NC patients. Surprisingly, PLMD and SDB have not been adequately addressed in the literature: most studies evaluated non-homogeneous populations of narcoleptic patients with and without cataplexy [7,8,4,11], or lacking hypocretin-1 measurements [5,9,10]; others did not synchronously assess movement and respiratory disturbances during sleep [3,4,9,10], or applied arbitrary or outdated definitions of these sleep disorders [3,4,6-8,11] (Table 1).

According to the guidelines on narcolepsy treatment of the European Federation of Neurological Societies (EFNS) and of the American Academy of Sleep Medicine (AASM) [12,13], coexistent sleep disorders must be taken into consideration and treated separately along with the specific narcolepsy therapy. Nevertheless, only few studies disclosed a negative impact of SDB and PLMD on nocturnal sleep continuity [6,10,11] or, even less, on EDS [10,11].

The aim of the present study was therefore to investigate the prevalence and the clinical relevance of SDB and PLMD in a well-described and homogeneous series of 36 consecutive hypocretin-deficient NC patients.

Patients and methods

We analysed sleep data (nocturnal videopolysomnography, VPSG, and multiple sleep latency test, MSLT) of 36 consecutive NC patients, referred to the Department of Neurology of the University Hospital of Zurich between January 2003 and November 2007. NC was diagnosed according to the International Classification of Sleep Disorders, 2nd edition (ICSD-2) [1]. Data collection was authorized by the local ethic committee, and patients signed a written informed consent. Patients, 50% males, had a mean age of 39±16 years and a mean body mass index (BMI) of 28±6 kg/m^2. In all patients, clinical examination and cerebral MRI were normal. They underwent a VPSG followed by MSLT and completed the Epworth sleepiness scale (ESS) for subjective EDS assessment [14]. Thirty-three patients were HLA-DQB1*0602 - positive (not available in 1 patient, 1 was DRB1*15 - positive), and 23 out of the 24 individuals, who underwent lumbar puncture, were hypocretin-1 deficient. Twenty-nine subjects were drug-naïve (diagnostic assessment), and 7 subjects were recorded after a wash-out period of 14 days from stimulant (4 patients), anticataplectic (2 patients) or combined (1 patient) treatment.

According to ICSD-2, patients with an apnea-hypopnea index (AHI) $\geq$ 5/h were considered to have SDB, and individuals with an index of periodic leg movements in sleep (PLMI) $\geq$ 15/h to have PLMD [1]. Conforming to AASM criteria, we further differentiated the severity of SDB into mild (AHI between 5 and 15/h), moderate (AHI between 15 and 30/h) and severe (AHI > 30/h) [15]. Clinical and VPSG features of patients with and without SDB and with and without PLMD respectively were compared (Mann-Whitney U test, Pearson Chi Square test). A p-value < 0.05 was considered statistically significant.

Results

Eleven patients (31%) were affected by SDB (figure). Mild SDB was diagnosed in 4 (11%) subjects, moderate SDB in another 4, and severe SDB in 3 (8%). One of the latter patients was a 78-year-old woman with significant cardiovascular comorbidities (arterial hypertension, diabetes mellitus type II, and ischemic stroke). In 5 out of 11 (46%) SDB patients, apneas were mostly obstructive, whereas in a single subject mostly of central origin. The remaining 5 patients (46%) showed mixed, obstructive and central apneas. In 2 women with moderate and severe obstructive SDB, apneas and hypopneas were mostly associated with REM sleep, whereas in the other 9 patients, apnea episodes mainly occurred during NREM sleep stages 1 and 2.

NC patients with SDB were significantly older (49±5 vs. 35±3 years; *p*-value=0.02), had a higher BMI (30±1 vs. 26±1 kg/m^2; *p*-value=0.04) and showed a higher PLMI (25±6 vs. 13±4, *p*-value=0.05), especially during light NREM sleep, than subjects without SDB. Additionally, SDB patients had a tendency towards larger amounts of NREM sleep stage 1 (21±12% vs. 15±5%, p=0.086) and less slow wave sleep (SWS) (9±7% vs. 14±6%, p=0.18). We could not detect any difference in gender distribution nor in EDS, although SDB was more often observed in males than in females (73% vs 40%, p=0.07) (Table 2).

Fourteen subjects (39%) had PLMD (Figure). We observed PLMs during REM sleep in 9 subjects, one of them with PLMs selectively during REM sleep (mean PLMI=2). PLMD subjects were older than patients without PLMD (50±4 vs. 32±2 years, p= 0.001) without any other significant clinical differences. PLMD patients showed lower sleep efficiency (82±12% vs. 92±6%, p=0.01), longer REM latency (102±135 vs 17±29 min, p=0.013), less total sleep time (353±66 vs. 398±31 min, p=0.007), a larger amount of NREM sleep stage 1 (20±11% vs 14±5%, p=0.05), a lower amount of NREM sleep stage 2 (36±11% vs 43±6%, p=0.05), and less sleep onset REM periods in the MSLT than patients without PLMD (Table 2).

Finally, SDB was associated with PLMD (p=0.006, Chi square test) (Figure). Despite the higher PLMI of patients with SDB, patients with PLMD did not reach statistically significant

differences in the respiratory parameters apart from an higher hypopnea index. Neither SDB nor PLMD were significantly associated with drug treatment (Table 1). A sub-analysis on the 23 NC patients with proved hypocretin deficiency yielded analogous results.

Discussion

Our study adopted for the first time currently accepted criteria to synchronously assess SDB and PLMD in an homogenous population of hypocretin-deficient narcoleptic patients with cataplexy free of medication. We obtained the following main findings: 1, SDB and PLMD are highly prevalent and mutually associated in NC, especially in older patients; 2, SDB and PLMD are rarely severe in NC; and 3, SDB and PLMD enhance nocturnal sleep disruption without clinically relevant correlations with daytime symptoms.

The prevalence of SDB in our NC population (11/36, 31%) is higher than in the general population [1], but this is in line with the reported prevalence (33/133, 25% with AHI>10/h) in the only study performed in NC patients [5]. The occurrence of SDB in NC patients with older age [11,5], and higher BMI [16], not only confirms previous studies in NC, but also mirrors the knowledge of SDB risk factors obtained in the general population [1,17]. Additionally, our predominantly obstructive (and mixed) SDB argue - together with the findings of Sansa et al [5] - against older findings of mainly central apneas [4], and further support the comorbidity of NC with mild to moderate nocturnal breathing disturbance [7,8]. Besides the intrinsic relation between BMI and SDB via upper airway obstruction, other pathophysiological mechanisms may contribute to the increased prevalence of SDB in NC. In fact, experimental models showed that hypocretin knockout mice have blunted hypercapnic ventilatory response during wakefulness with increased sleep apneas [18], and reduced long term facilitation after exposure to intermittent hypoxia [19]. Moreover, hypocretin neurons are activated by CO_2 inhalation [20], and increase pre-inspiratory hypoglossal motor activity thus decreasing upper airway resistance during inspiration [21].

Thirty-nine % (14/36) of our NC patients suffer from PLMD, a prevalence significantly higher compared to that of the general population and comparable with the two previous reports [9,10], further corroborating the evidence of motor control impairment during both NREM and REM sleep in NC. In this context, the association between SDB and PLMD is a new finding in NC (table 1), with the potential of each sleep related movement or respiratory event to induce a shift to a lighter sleep stage where they more frequently occur. Therefore, SDB and PLMD mutually interact to disrupt nocturnal sleep continuity and enhance sleep-wake instability, but the contribution of these two disorders to EDS in NC appears to be negligible. Intriguingly, patients without PLMD showed a mildly higher number of sleep onset REM periods at the MSLT, a finding potentially linked to a negative correlation between sleep onset REM periods and age (Pearson's correlation coefficient: -0.55, p=0.002), as already reported [22].

We also highlight that only a minority of NC patients have severe SDB or PLMD, which may have a true therapeutic implication, thus probably explaining, together with the scarce impact on EDS, the commonly found insufficient compliance to CPAP treatment in NC [5,16]. Nevertheless, the two disorders should be appropriately treated, especially in severe cases, [12,13], in light of their potential contribution to cardiovascular risk [23,24]. Concerning the therapy of narcolepsy's core symptoms, e.g. EDS, only the use of NC-specific medication appears to lead to a clinically significant improvement.

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Figure: distribution of sleep disordered breathing (upper part), of periodic limb movement severity (middle part), and association between SDB and PLMD (lower part) in the 36 NC patients.

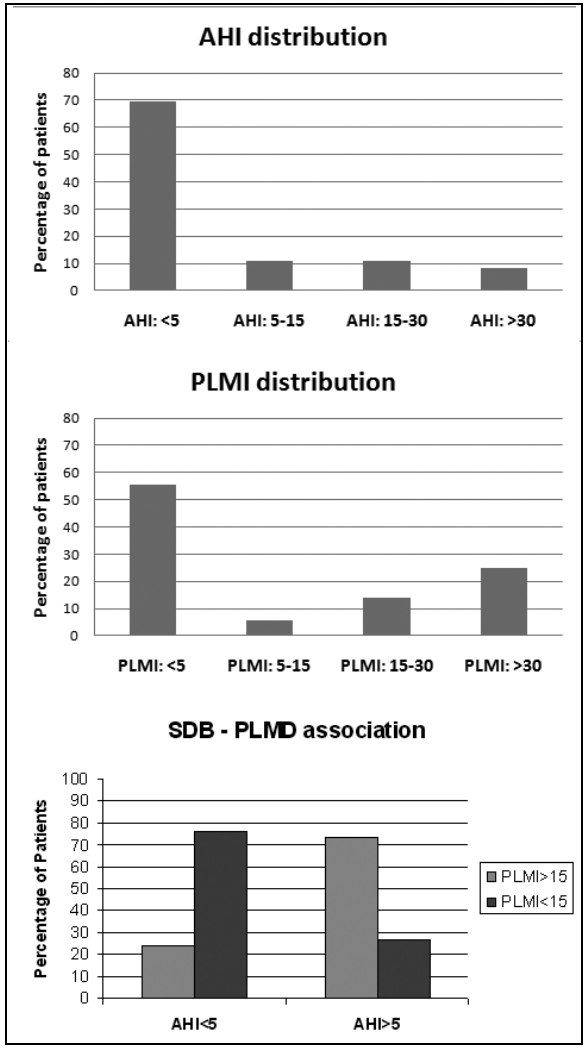

Table 1: sleep disordered breathing and periodic leg movements during sleep in different studies of narcoleptic patients

Study	Population	SDB	AHI>5	AHI>30	PLMD	PLMI>5	PLMI>15	Limitations	Associations
Laffont, 1978	18 pts	28%	n.a.	n.a.	n.a.	n.a.	n.a.	Absent cut-off for SDB definition; Unavailable hcrt.	n.a.
Wittig, 1983	57 pts	5%	5% (OAI>25)	n.a.	25%	n.a.	n.a.	PLMD defined by ≥ 3 series of 30 PLMs; SDB defined by OAI>25; unavailable hypocretin-1.	PLMD associated with ↑awakenings, ↑WASO, ↑NREM1, and older age; SDB associated with ↑WASO, ↑NREM1.
Mosko, 1984	92 pts	10%	10% (AI>5)	n.a.	49%	n.a.	n.a.	Patients with and without cataplexy; PLMD defined by 15% of TST with PLMs; unavailable hypocretin-1.	9% of patients with PLMD showed SDB
Baker, 1986	177 pts	13%	13% (AI>5)	n.a.	63% (I); 46% (II); 26% (III)	n.a.	n.a.	Patients with and without cataplexy; PLMD defined with different criteria; unavailable hypocretin-1.	n.a.
Chokroverty, 1986	16 pts	69%	n.a.	n.a.	n.a.	n.a.	n.a.	Patients with and without cataplexy; Daytime PSG; Absent cut-off for SDB definition¸ unavailable hypocretin-1.	n.a.
Harsh, 2000	530 pts	19%	19%	n.a.	n.a.	46%	n.a.	Patients with and without cataplexy; Hypocretin-1 not reported; PLMD defined as PLMI>5; unavailable hypocretin-1.	SDB and PLMD in older patients; PLMD associated with ↑arousal index, awakenings, NREM1, SWS, ↓SE, and higher EDS (at MWT); SDB with ↑awakenings, ↑NREM1, ↓SWS and higher EDS (at ESS).
Sansa, 2009	133 pts	25%	25% (AHI>10)	n.a.	n.a.	n.a.	n.a.	Hypocretin-1 not reported; SDB defined as AHI>10.	OSAS associated with male gender, ↑age and BMI.

Ferri, 2006	40 pts	n.a.	n.a.	n.a.	48%	70%	48%	Hypocretin-1 not reported.	Different periodicity of PLMS compared with RLS pts and controls.
Dauvilliers, 2007	169 pts	n.a.	n.a.	n.a.	53%	67%	n.a.	Hypocretin-1 not reported, PLMD defined as PLMI>10.	PLMD associated with older age, ↑NREM1, ↓REM, higher EDS (MSLT)
Present Study	36 pts	31%	31%	8%	39%	44%	39%		SDB associated with older age and higher BMI; PLMD associated with older age, ↓SE, ↓TST; SDB associated with PLMD.

Table Legend:

SDB, sleep-disordered breathing; PLMD, periodic limb movement disorder; PLMs, periodic limb movements during sleep; OAI, obstructive apnea index; WASO, wakefulness after sleep onset; NREM1, Non-REM sleep stage 1; AI, apnea index; TST, total sleep time; I=PLMD defined with at least 1 series of ≥ 5 PLMs; II= PLMD defined with al least ≥ 40 PLMs per night; III= PLMD defined with al least ≥ 100 PLMs per night; PSG, polysomnoraphy; SWS, slow wave sleep; SE, sleep efficiency; EDS, excessive daytime sleepiness; MWT, maintenance of wakefulness test; ESS, Epworth sleepiness scale; BMI, body mass index; RLS, restless legs syndrome; REM, REM sleep; MSLT, multiple sleep latency test.

Table2: Demographic, polysomnographic and MSLT data of NC patients

	AHI<5		AHI>5		*p-value*	PLMI<15		PLMI>15		*p-value*
	Mean	***SD***	***Mean***	***SD***		***Mean***	***SD***	***Mean***	***SD***	
Patient Number	25		11			22		14		
Male Sex (%)	40%		73%		*ns*	41%		64%		*ns*
Age	34.9	13.5	49.2	16.5	*0.015*	32.4	11.1	50.2	16.1	*0.001*
Drug treatment (%)	12%		36%		*ns*	18%		29%		*ns*
BMI	26.5	6.0	30.4	4.8	*0.038*	27.8	6.9	27.6	3.9	*ns*
ESS	16	3.8	15.6	4.4	*ns*	15.0	3.3	17.2	4.6	*ns*
TST (min)	384.1	52.9	371.9	52.1	*ns*	398.1	31.1	352.6	66.5	*0.007*
SE (%)	88.6	10.4	86.3	8.9	*ns*	91.7	5.7	82.1	12.4	*0.01*
SL (min)	13.7	12.9	10.9	21.3	*ns*	13.4	12.4	11.9	20.4	*ns*
REM L (min)	26.2	44.6	103.2	149.8	*ns*	16.7	28.6	101.6	135.5	*0.013*
NREM1 (%)	14.9	5.4	21.3	11.7	*ns*	14.5	5.5	20.5	10.6	*0.05*
NREM2 (%)	41.6	8.4	38.4	10.5	*ns*	43.4	6.4	36.2	10.9	*0.05*
NREM3 (%)	13.8	6.4	9.5	6.8	*ns*	14.4	5.8	9.5	7.1	*ns*
REM (%)	18.5	7.2	17.1	11.1	*ns*	19.4	7.3	15.9	9.9	*ns*
Central AI	0.2	0.4	3.1	5.4	*0.013*	1.3	4.1	0.6	0.9	*ns*
Mixed AI	0.1	0.1	2.4	3.6	*<0.0001*	0.7	2.4	0.9	1.9	*ns*
Obstructive AI	0.2	0.4	5.9	5.8	*<0.0001*	1.1	2.4	3.2	5.8	*ns*
Hypopnea Index	0.8	0.9	10.3	7.1	*<0.0001*	2.2	3.8	6.0	7.7	*0.036*
AHI	1.2	1.3	21.7	14.4	*<0.0001*	5.4	11.2	10.8	13.7	*ns*
Arousal Index	10.3	5.1	11.9	8.2	*ns*	10.5	5.9	11.4	6.7	*ns*
PLMI	12.7	22.7	25.4	19.8	*0.046*	1.2	2.6	40.7	17.7	*<0.0001*
PLMI in NREM1	9.5	21.6	22.1	17.5	*0.011*	1.1	3.1	33.3	23.3	*<0.0001*
PLMI in NREM2	17.8	30.8	30.8	30.5	*0.049*	1.9	4.3	54.8	27.4	*<0.0001*
PLMI in NREM3	28.1	60.4	73.6	100.5	*ns*	1.4	5.6	108.1	91.2	*<0.0001*
PLMI in REM	1.2	2.5	6.8	10.3	*ns*	0.3	1.6	6.8	8.8	*<0.0005*
MSLT SL (min)	2.1	1.5	1.8	1.3	*ns*	2.0	1.6	1.9	1.3	*ns*
MSLT REM L (min)	3.8	2.3	5.4	3.7	*ns*	3.8	2.1	5.2	3. 7	*ns*
SOREMPs	3.4	0.8	3.3	1.0	*ns*	3.6	0.6	2.9	1.1	*0.043*

Table legend:

BMI = body mass index, ESS = Epworth Sleepiness Scale, TST = total sleep time, SE = sleep efficiency, SL = sleep latency, REM L = REM latency, NREM= non-REM sleep stage, AI = apnea index, AHI = apnea hypopnea index, SpO_2= peripheral oxygen saturation, PLMI = periodic limb movement index, SOREMPs= Sleep onset REM periods.